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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/513,365	02/25/2000	Curtis C. Harris	15280-376100US	7045

7590 12/18/2001

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EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/18/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/513,365	HARRIS ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *10-19 and 22-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Election filed October 12, 2001 (Paper No. 13) in response to the Office Action of September 10, 2001 is acknowledged and has been entered. Claims 1-57 are pending in the application and Claims 10-19,22-57 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-9, and 20-21 are currently under prosecution.

Applicant's election with traverse of Group I, claims 1-9, 20-21 in Paper No 13 is acknowledged. The traversal is on the ground(s) that the inventions all stem from a common concept and theory, and are thus related. As such, applicants argue that prosecution of Groups I-XI would not place a substantially greater burden on the Examiner. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in Paper No. 11. As to the question of burden of search, the inventions are classified differently, necessitating different searches and patentability issues. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6, 8-9 are indefinite for reciting "stringent hybridization conditions" (Claim 6), "stringent conditions" (Claim 8), and "moderately stringent hybridization conditions" (Claim 9). Stringent and or moderately stringent conditions are not defined by the claim. Furthermore, the specification (page 21) does not contain a limited definition of what is defined by such conditions. The speciation only teaches that which is considered "exemplary" stringent or moderately stringent conditions. Thus, stringent conditions read on the full range of stringent conditions, that is from very permissive to very high stringency. Hence, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and would not be able to determine the metes and bounds of the claims. This rejection can be obviated by distinctly defining the conditions of stringency in the claims.

Claim 6 is further rejected as vague because it is not clear how applicant is further limiting the isolated nucleic acid being claimed. It is further not clear what is meant by "same sequence"-same sequence as what? Also, the specification does not define what is included or excluded as "degenerate primer sets". As written, the metes and bounds of the claim cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5-9, and 20-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid comprising a nucleotide sequence of SEQ ID NO:2, or an isolated nucleic acid which encodes a polypeptide comprising an amino acid sequence of SEQ ID NO. 1, does not reasonably provide enablement for the claims as broadly drawn. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to isolated nucleic acids encoding a tumor suppressor polypeptide p33ING2, wherein the polypeptide has greater than 70% amino acid sequence identity to a polypeptide comprising an amino acid sequence of SEQ ID NO:1, wherein the polypeptide selectively binds to polyclonal antibodies generated against a polypeptide comprising an amino acid sequence of SEQ ID NO:1, wherein the nucleic acid is from a human, wherein the nucleic acid is amplified by primers that selectively hybridize under stringent

hybridization conditions to the same sequence as degenerate primers encoding amino acid sequences selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO:4, wherein the nucleic acid encodes a polypeptide having a molecular weight of about 28 kDa to about 38 kDa, further including expression vectors, and host cells thereof. The claims are further drawn to an isolated nucleic acid encoding a tumor suppressor polypeptide, P33ING2 that specifically hybridizes under moderately or stringent conditions to a nucleic acid comprising a nucleotide sequence of SEQ ID NO:2.

This includes a whole universe of nucleic acids encoding polypeptides with greater than 70% identity to SEQ ID NO.1 and further having a molecular weight of about 28 kDa to about 38 kDA. This further encompasses all nucleic acids that hybridize under any conditions to any polynucleotide with any degree of complementarity to SEQ ID NO:2.

The specification teaches (page 8) that the nucleotide sequence of p33ING2 (SEQ ID NO:2) encodes a nuclear protein having a molecular weight of approximately 33 kDa and comprises approximately 270 amino acids (SEQ ID NO:1). The specification further teaches that p33ING2 represents a nuclear protein involved in the regulation of cell proliferation, cellular aging, anchorage, and apoptosis and represents a new tumor suppressor. However, the specification also teaches (page 10, line 15) that the term p33ING2 refers to polymorphic variants, alleles, interspecies homologs, and mutants which have about 70% amino acid sequence identity, preferably about 80-90% amino acid sequence identity to SEQ ID NO:1 over a window of about at least 50-100 amino acids. Mutants of p33ING2 (page 11) can be due to truncation, elongation, substitution of amino acids, deletion, insertions or lack of expression due to promoter or splice site mutations. The specification further teaches that a mutant has activity that differs

from the activity of wildtype p33ING2 by at least about 20% as measured using an assay disclosed. The specification further teaches that degenerate primer sets (page 25, line 20) can be used to amplify and isolate a nucleic acid encoding p33ING2, from DNA or RNA.

Thus, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a whole universe of nucleic acids which encode a polypeptide or polypeptide fragments with sequence homology (greater than 70%) absent the biological properties representative of what is claimed, and applicant has not enabled all of these types of modified proteins because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed.

Those of skill in the art recognize that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the encoded protein to function as claimed. While it is known that many amino acid substitutions are possible in any

given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all such encoded polypeptides and or fragments thereof with sequence similarity to the amino acid sequence of SEQ ID NO. 1.

With regards to nucleic acids hybridizing to SEQ ID NO:2, one cannot extrapolate the teaching of the specification to the scope of the claims because the specification does not provide teachings or working examples which would provide sufficient guidance to allow one of skill in the art to use the multitude of polynucleotide sequences encompassed by the scope of the claims. Further, the hybridization conditions as disclosed by the specification are not limiting and thus the claims read on the full range of conditions from low to highly stringent and thus the claimed hybridized polynucleotides read on polynucleotides that range from those that lack significant complementarity to those that are completely complementary to the claimed polynucleotide. Therefore, in view of the breadth of the claims, the general teachings of the art, and the absence of working examples, it would require undue experimentation for one skilled in the art to use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Shimada *et al.* (Cytogenet. Cell. Genet. Vol. 83: pages 232-235, 1988, IDS) as further evidenced by the sequence listing attached at the end of the action. (It is assumed that Shimada *et al.* is a 102(b) reference since it was published in 1998 and the publication month is unknown. In the event that applicants provide evidence that the reference is not a 102(b)- then the rejection will be maintained as a 102(a)).

Shimada *et al.* teach an isolated nucleic acid encoding a tumor suppressor polypeptide wherein the polypeptide has greater than 70% amino acid sequence identity to a polypeptide comprising an amino acid sequence of SEQ ID NO:1, wherein the nucleic acid is from a human, and wherein the nucleic acid comprises a nucleotide sequence of SEQ ID NO:2. Further, in view of the fact that Shimada *et al.* have isolated the gene such a gene would comprise complementary DNA which reads on isolated nucleic acids that specifically hybridizes under stringent or moderately stringent conditions to a nucleic acid comprising a nucleotide sequence of SEQ ID NO:2. Further, though Shimada *et al.* does not teach that the encoded polypeptide selectively binds to polyclonal antibodies generated against a polypeptide comprising an amino acid sequence of SEQ ID NO:1 or that the isolated nucleic acid is amplified by primers that

selectively hybridize under stringent hybridization conditions to the same sequence as degenerate primers encoding amino acid sequences selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO:4, or that the nucleic acid encodes a polypeptide having a molecular weight of about 28 kDa to about 38 kDa, the claimed nucleic acid appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. The claims read on the product *per se*, an isolated nucleic acid, which is taught in the art of record.

Claims 1-2, 6-9, 20-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonaldo *et al.* (Genbank Database, Accession No. BF523624, as published in Genome Research, Vol. 6, (9), 1996).

Bonaldo *et al.* teach an isolated nucleic acid encoding a polypeptide wherein the polypeptide has greater than 70% amino acid sequence identity to a polypeptide comprising an amino acid sequence of SEQ ID NO:1. Bonaldo *et al.* further teach an expression vector (pT7T3D-Pac) and host cell (DH10B). Further, the sequences of Bonaldo *et al.* would inherently comprise complementary DNA which reads on isolated nucleic acids that specifically hybridizes under stringent or moderately stringent conditions to a nucleic acid comprising a nucleotide sequence of SEQ ID NO:2 since Bonaldo *et al.* teach that the subtracted library was PCR amplified. Further, though Bonaldo *et al.* does not teach that the encoded polypeptide is a tumor suppressor and or selectively binds to polyclonal antibodies generated against a polypeptide comprising an amino acid sequence of SEQ ID NO:1; or that the isolated nucleic acid is

amplified by primers that selectively hybridize under stringent hybridization conditions to the same sequence as degenerate primers encoding amino acid sequences selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO:4, or that the nucleic acid encodes a polypeptide having a molecular weight of about 28 kDa to about 38 kDa, the claimed nucleic acid appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. The claims read on the product *per se*, an isolated nucleic acid, which is taught in the art of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimada *et al.*

Shimada *et al.* teach as set forth above.

Shimada *et al.* do not include an expression vector and host cell.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to include an expression vector and host cell with the teachings of Shimada *et al.* One would have been motivated to do so as such techniques are well known and art-standard in recombinant DNA technology, and there would have been a reasonable expectation of success at analyzing the expressed product from a host cell.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
December 11, 2001